Topochemical Models for Prediction of Anti-tumor Activity of 3-Aminopyrazoles

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Relationship between topochemical indices and inhibition of CDK2/cyclin A by 3-aminopyrazoles was investigated using a data set comprising of 42 3-aminopyrazoles. Three topochemical indices—the *Wiener's topochemical index*–a distance based topochemical index, *atomic molecular connectivity index*–an adjacency based topochemical index and *superadjacency topochemical index*–an adjacency-cum-distance based topochemical index were used for the present investigations. The values of Wiener's topochemical index, atomic molecular connectivity index and superadjacency topochemical index for each of the 42 compounds comprising the data set were computed using an in-house computer program. Resultant data was subsequently analyzed and suitable models were developed after identification of the active ranges. Subsequently, a biological activity was assigned to each of the compounds using these models, which was then compared with the reported CDK2/cyclin A inhibitory activity. High accuracy of prediction ranging from 86 to 89% was observed using these models.

Key words Wiener's topochemical index; superadjacency topochemical index; CDK2/cyclin A; 3-aminopyrazole; topochemical model; anti-tumor agents

Graph theory has been used for modeling chemical structures, that is, chemical compounds, intermediates, changes and mechanisms.[1)] Over the past decades graph-based molecular structure descriptors have developed into a quite active field. In these applications a molecular structure is identified to a graph, with vertices representing non-H atoms and edges representing chemical bonds.[2)] During the last decade the interest in the problem of computer-aided design of organic structures with prescribed properties has significantly increased.[3)] Today, the information feeding the drug design effort is increasingly quantitative, based upon recent developments in molecular structure description, combinatorial mathematics, statistics, and computer simulations.[4)] In chemistry, a graph represents the topology of a molecule in the sense that it depicts the pattern of connectedness of atoms in the molecule, being, at the same time, independent of such metric aspects of molecular structure as equilibrium distance between nuclei, bond angles, *etc.*[5)] Topological indices or graph invariants are the single numbers for characterization of molecular structures.[6)] In recent years a large number of topological indices have been reported and utilized for chemical documentation, isomer discrimination, study of molecular complexity, chirality, similarity/dissimilarity, QSAR/QSPR, drug design and database selection, lead optimization, rational combinatorial library design and for deriving multilinear regression models.[7—10)] Though a large number of topological indices have been reported in literature but only some of them have been successfully employed in SAR studies. Notable amongst these are Wiener's index,[11,12)] Hosoya's index,[13,14)] Randic's molecular connectivity index, χ,[15)] the higher-order connectivity indices, ${}^{n}\chi$, for the paths of length n defined by Kier and Hall,[16)] Balaban's index, J,[17—20)] Zagreb group parameters, M_1 and M_2,[21)] eccentric connectivity index,[22—26)] eccentric adjacency index[27,28)] and superpendentic index.[29)] Topochemical indices are the topological indices derived from the chemical graphs and modified so as to take into consideration the presence and relative position of heteroatom. Topochemical indices that have been reported and used for SAR studies include atomic molecular connectivity index,[30)] eccentric adjacency topochemical index,[31)] Wiener's topochemical index[32,33)] and superadjacency topochemical index.[34,35)]

The importance of cyclin-dependent kinases (CDKs) in cell cycle regulation, their interaction with oncogenes and tumor suppressors, and their frequent deregulation in human tumors, has encouraged an active search for agents capable of perturbing the function of CDKs.[36)] Therefore, inhibition of cyclin-dependent kinases is a theme of major interest in current anti-cancer agents' research. Different classes of chemical inhibitors of these enzymes have been identified during the past decade and the structural basis of inhibition has been elucidated by X-ray crystallography studies of one member of the family, CDK2.[37)] The CDK2 protein can form complexes with both cyclins E and A, and it is required for the G1/S transition and S phase progression and centrosome duplication.[38)] One of the key CDK2 substrates is the E2F-1 protein itself, of which the turnover and activity is induced by phosphorylation by CDK2/cyclin A. This leads to higher than normal levels of E2F, which have been found to induce apoptosis.[39)] The series of compounds used in this study is a novel class of CDK2/cyclin A inhibitors which was discovered by HTS and have demonstrated tumor growth inhibition in a xenograft model of human ovarian cancer. Amongst these, the lead compound **41** has been reported to have potential to inhibit CDK2/cyclins E and A in an *in vivo* setting.[39)] Therefore this series of compounds have the potential for optimization and development of a compound as drug for the treatment of human cancers.

In the present study three topochemical indices *i.e. Wiener's topochemical index*–a distance based topochemical descriptor, *atomic molecular connectivity index*–an adjacency based topochemical descriptor and *superadjacency topochemical index*–an adjacency-cum-distance based topochemical descriptor have been used for development of models for prediction of CDK2/cyclin A inhibition by 3-aminopyrazoles.

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Methodology

Calculation of Topochemical Indices The *Wiener's Topochemical Index* is defined as the sum of the chemical distances between all the pairs of vertices in hydrogen suppressed molecular graph, that is

$$W_c = \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} P_{ij}^{c}$$

where, P_{ic} is the chemical length of the path that contains the least number of edges between vertex i and vertex j in the graph G; n is the maximum possible number of i and j. Wiener's topochemical index (W_c) can be easily calculated from the chemical distance matrix of a hydrogen suppressed molecular structure. This matrix is obtained by substituting, row elements corresponding to heteroatom, with relative atomic weight with respect to carbon atom.[32,33]

The *Atomic Molecular Connectivity Index* (AMCI) is the modification of path-one molecular connectivity index. It takes into consideration the influence of heteroatom and is defined as the summation of the modified bond values of adjacent vertices for all edges in the hydrogen suppressed molecular graph. It is denoted by χ^A and is expressed as

$$\chi^A = \sum_{i=1}^{n} (V_i^c V_j^c)$$

where, n is the number of vertices, V_i^c and V_j^c are the modified degrees of adjacent vertices i and j forming the edge $\{i,j\}$ in a graph G. The modified degree of a vertex can be obtained from the adjacency matrix by substituting row element corresponding to heteroatom, with relative atomic weight with respect to carbon atom.[30]

The *Superadjacency Topochemical Index* is defined as the sum of the products of the concerned vertex chemical degree and the sum of the adjacent vertex chemical degrees divided by the chemical eccentricity of the concerned vertex, over all the vertices in the hydrogen suppressed molecular graph. It is denoted by $\int^{Ac}$ and is expressed as

$$\int^{Ac} = \sum_{i=1}^{n} \frac{\deg V_i^c * S_{ic}}{E_{ic}}$$

$$S_{ic} = \sum \deg V_j^c$$

Where, S_{ic} is the sum of chemical degrees of all vertices (v_j), adjacent to vertex i and n is the number of vertices in graph G.

For a molecular graph (G), $v_1, v_2, \ldots, v_n$ are vertices, the number of first neighbors of a vertex v_i is the chemical degree of this vertex and is denoted by deg(v_{ic}). The chemical distance dc ($v_i, v_j \mid G$) between the vertices v_i and v_j of G is the length of the shortest path connecting v_i to v_j. While, chemical eccentricity E_{ic} of vertex v_i, in graph G is the length of the shortest path from v_i to vertex v_j that is farthest from v_i ($E_{ic} = \max dc(v_i, v_j); j \mid G$). Superadjacency topochemical index is calculated from the chemical distance matrix (D^c), the chemical adjacency matrix (A^c) and a new matrix, the additive chemical adjacency matrix ($A^{\alpha c}$), obtained by modifying A^c. Chemical distance matrix is utilized for deriving chemical eccentricity while chemical adjacency matrix is utilized for deriving chemical degree of vertices. When non-zero row elements in chemical adjacency matrix represent the chemical degree of corresponding vertex in a molecular graph, the matrix may be defined as the additive chemical adjacency matrix. This matrix is utilized for deriving S_{ic} for the corresponding vertex.[34]

Model Development

A dataset[38] comprising of 42, 3-aminopyrazoles having inhibitory activity against CDK2/cyclin A was selected for the development of model for the present investigation. The basic structure of these compounds is presented in Fig. 1 and various substituents enlisted in Table 1. The data set comprised of both active and inactive compounds. The values of Wiener's topochemical index were computed for all the compounds involved in the data set using an in-house computer program. For the selection and evaluation of range specific features, exclusive activity ranges were discovered from the frequency distribution of response level. Resulting data was analyzed and a suitable model was developed after identification of the active range by maximization of the moving average with respect to the active compounds (<35%=inactive, 35–65%=transitional, ≥65%=active).[40,41] Subsequently, each analogue involved in the data set was assigned a biological activity using this model which was then compared with the reported CDK2/cyclin A inhibitory activity. The activity of these compounds was reported in terms of IC_{50} (nM). For the purpose of this study, the compounds having IC_{50} less than 100 nM were considered to be active while those having IC_{50} (nM) greater than 100 were considered as inactive. The percentage degree of prediction of a particular range was derived from the ratio of the number of compounds predicted correctly to the total number of compounds present in that range. The overall degree of prediction was derived from the ratio of the total number of compounds predicted correctly to that of the total number of compounds present in both the active and inactive ranges.

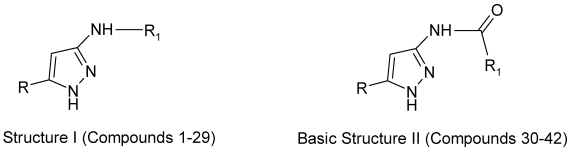

Fig. 1. Basic Structures of 3-Aminopyrazoles

The aforementioned procedure was similarly adopted for *atomic molecular connectivity index*, χ^A and *superadjacency topochemical index*, $\int^{Ac}$. The results are summarized in Table 2.

Results and Discussion

The recognition of cyclin-dependent kinase (CDK)/cyclin complexes by various cell-cycle regulatory proteins, including certain tumor suppressors and transcription factors, occurs at least in part through a protein–protein interaction with a binding groove on the cyclin subunit. Since CDK function is generally deregulated in tumor cells, blocking of this recruitment site prevents recognition and subsequent phosphorylation of CDK substrates and offers a therapeutic approach towards restoration of checkpoint control in transformed cells.[42] 3-Aminopyrazoles have been recently identified as a class of CDK2/cyclin A/E inhibitors and have been reported to have potential for optimization. One major advantage of this series of compounds is that they are potent inhibitors of CDK2/cyclin A since they are effective in nanomolar quantities.

Topological/topochemical models are now considered as powerful tools for the prediction of physicochemical and biological properties of molecules. By using graph theoretic invariants as descriptors, one can utilize a set of well-understood mathematical properties to describe more complex physicochemical and biological behavior of molecules.[32] In pharmaceutical chemistry such methods are used for screening compounds to be tested for specific activity,[43] lead identification and lead optimization[8] mainly because these methods are rapid and cost-effective.

In the present study, models using three topochemical indices, *viz.* Wiener's topochemical index, AMCI and superadjacency topochemical index have been developed for the prediction of CDK2/cyclin A inhibitory activity of this series of compounds. The idea behind choosing these three indices

Table 1. Relationship of Wiener's Topochemical Index (W_c), AMCI (χ^A) and Superadjacency Topochemical Index ($\int^{Ac}$) with CDK2/Cyclin A Inhibition by 3-Aminopyrazoles

Comp. No.	Substituent		Index value			CDK2/cyclin A inhibition			
						Assigned			Reported
	R	R_1	W_c	χ^A	$\int^{Ac}$	W_c	χ^A	$\int^{Ac}$	
1	Methyl	Phenyl	408.86	6.99	27.18	−	−	±	−
2	Methyl	Propyl	231.10	5.45	22.51	−	−	−	−
3	Cyclopropyl	Propyl	352.94	6.53	26.13	−	−	±	−
4	Cyclopropyl	Phenyl	585.70	8.07	30.04	−	−	±	−
5	Cyclopropyl	4-Br–C_6H_4–	740.79	7.89	26.02	−	−	±	+
6	Cyclopropyl	4-Cl–C_6H_4–	709.26	8.15	27.76	−	−	+	+
7	Cyclopropyl	4-OMe–C_6H_4–	826.20	8.84	28.35	±	±	+	−
8	Cyclopropyl	4-COOH–C_6H_4–	950.79	9.23	29.69	±	±	±	−
9	Cyclopropyl	4-$CONH_2$–C_6H_4–	949.21	9.26	29.54	±	±	+	+
10	Cyclopropyl	3-Br–C_6H_4–	729.79	7.89	27.68	−	−	+	−
11	Cyclopropyl	3-Cl–C_6H_4–	698.26	8.15	29.81	−	−	±	−
12	Cyclopropyl	3-OMe–C_6H_4–	804.20	8.84	30.27	−	±	±	−
13	Cyclopropyl	3-CF_3–C_6H_4–	1061.85	9.37	33.95	±	±	−	−
14	Cyclopropyl	2-Br–C_6H_4–	718.79	7.93	31.71	−	−	±	−
15	Cyclopropyl	2-Cl–C_6H_4–	687.26	8.18	32.76	−	−	−	−
16	Cyclopropyl	2-OMe–C_6H_4–	782.20	8.86	32.99	−	±	−	−
17	Cyclopropyl	2,6-diCl–C_6H_4–	794.78	8.30	37.60	−	−	−	−
18	Cyclopropyl	3,4-diCl–C_6H_4–	826.78	8.30	33.20	±	±	−	+
19	Cyclobutyl	4-Br–C_6H_4–	861.71	8.39	25.44	±	±	±	+
20	Cyclopentyl	4-Br–C_6H_4–	984.63	8.89	25.89	±	±	±	+
21	Cyclohexyl	4-Br–C_6H_4–	1127.55	9.39	25.35	±	±	−	−
22	Methyl	4-Br–C_6H_4–	535.95	6.81	24.36	−	−	−	−
23	Ethyl	4-Br–C_6H_4–	637.87	7.35	23.90	−	−	−	−
24	Propyl	4-Br–C_6H_4–	756.79	7.85	23.35	−	−	−	−
25	Isopropyl	4-Br–C_6H_4–	741.79	7.72	24.81	−	−	−	−
26	*sec*-Butyl	4-Br–C_6H_4–	863.71	8.26	24.38	±	−	−	−
27	*tert*-Butyl	4-Br–C_6H_4–	847.71	8.03	25.96	±	−	±	−
28	Phenyl	4-Br–C_6H_4–	1127.55	9.39	25.35	±	±	−	−
29	Benzyl	4-Br–C_6H_4–	1318.47	9.87	24.57	+	+	−	−
30	Cyclopropyl	Phenylacetyl	714.62	8.54	27.63	−	±	+	+
31	Cyclopropyl	4-$CONH_2$-phenylacetyl	1128.38	9.74	27.30	+	+	+	+
32	Cyclopropyl	3-OMe-phenylacetyl	964.62	9.32	28.11	±	±	+	+
33	Cyclopropyl	4-(2-Pyrrolidin-1-yl)-ethoxy	837.70	8.78	29.11	±	±	+	+
34	Cyclopropyl	4-OCF_3-phenylacetyl	1458.10	10.21	29.98	+	+	±	+
35	Cyclopropyl	4-Biphenylacetyl	1596.14	11.51	29.67	+	+	+	+
36	Cyclopropyl	4-(3-Fluorobiphenyl)acetyl	1756.05	11.79	30.32	+	+	±	+
37	Cyclopropyl	4-(3-Methylbiphenyl)acetyl	1749.06	11.90	30.72	+	+	±	+
38	Cyclopropyl	4-(4-Carboxybiphenyl)acetyl	2223.56	12.67	29.66	+	+	+	+
39	Cyclopropyl	4-(4-Carboxamidobiphenyl)acetyl	2221.40	12.70	29.55	+	+	+	+
40	Cyclopropyl	4-(2-Thenyl)-phenylacetyl	1429.56	10.52	32.14	+	+	±	+
41	Cyclopropyl	4-(2-Naphthyl)acetyl	1228.30	10.51	30.01	+	+	±	+
42	Cyclopropyl	4-(1-Naphthyl)acetyl	1180.30	10.53	32.53	+	+	±	+

+, active compound; −, inactive compound; ±, compound in the transitional range where activity could not be specifically assigned.

was that these indices provide structural information on three different concepts: Wiener's topochemical index is based upon inter-atomic distances and any increase in linearity and molecular size results in increase in the value of Wiener's topochemical index. The atomic molecular connectivity index, on the other hand, is based upon adjacency or connectivity of atoms with in a molecule. The value of AMCI increases not only with linearity and molecular size but also with cyclization. The superadjacency topochemical index is both adjacency as well as distance based. As a consequence of this, the value of this index tends to increase with the molecular size, branching as well as with cyclization.

Retrofit analysis of the data in Tables 1 and 2 reveal the following information with regard to the corresponding indices.

Model Based upon *Wiener's topochemical index*:

- Out of total 42 compounds, 29 were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 86.2% with regard to CDK2/cyclin A inhibitory activity.
- The active range had *Wiener's topochemical index* values greater than 1128. 10 out of 11 compounds in the active range exhibited CDK2/cyclin A inhibitory activity. The average IC_{50} of the correctly predicted compounds was 30.3 nM, indicating high potency of the active range.
- The inactive range had index values of <826. 15 out of 18 compounds (83%) in the inactive range were found to be inactive. Average IC_{50} value of the inactive range was found to be 2972 nM.
- Presence of a transitional range having *Wiener's topochemical index* values of 757 to 1128 indicated the gradual change in biological activity. The average IC_{50} was

Table 2. Models for Prediction of CDK2/Cyclin A Inhibition by 3-Aminopyrazoles

Model index	Nature of range in proposed model	Index value	Number of compounds falling in the range		Percent accuracy of range	Average IC_{50} (nM)		Overall accuracy of prediction
			Total	Correct		Total	Correct	
W_c	Inactive	<826.00	18	15	83.3	2486.17	2972.27	
	Transitional	826.00—1128.00	13	N.A.	N.A.	2521.92	N.A.	86.2
	Active	>1128.00	11	10	90.9	936.84	30.30	
χ^A	Inactive	<8.27	16	14	87.5	2756.44	3141.71	
	Transition	8.27—9.72	15	N.A.	N.A.	2228.87	N.A.	88.9
	Active	>9.72	11	10	90.9	936.64	30.30	
$\int^{Ac}$	Lower inactive	<25.35	9	9	100	5386.67	5386.67	
	Lower transitional	25.35—27.29	6	N.A.	N.A.	1983.00	N.A.	
	Active	27.30—29.67	11	9	81.8	196.82	52.22	88.0
	Upper transitional	29.68—32.74	11	N.A.	N.A.	337.54	N.A.	
	Upper inactive	>32.74	5	4	80.0	4316.60	5375.00	

W_c, Wiener's topochemical index; χ^A, atomic molecular connectivity index; $\int^{Ac}$, superadjacency topochemical index.

found to be 2521.92 nM for the compounds in the transitional range.

Model Based upon *Atomic molecular connectivity index (AMCI)*:

- Out of total 42 compounds, 27 compounds were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 88.9% with regard to CDK2/cyclin A inhibitory activity.
- The active range had *AMCI* values greater than 9.72. 10 out of 11 compounds in the active range exhibited CDK2/cyclin A inhibitory activity. The average IC_{50} of the correctly predicted compounds was 30.3 nM, indicating high potency of the active range.
- The inactive range with index values of <8.27 was observed. 14 out of 16 compounds (87.5%) in this range were found to be inactive. Average IC_{50} value of the inactive range was found to be 3142 nM.
- Presence of a transitional range having AMCI values of 757 to 1128 indicated the gradual change in biological activity. The average IC_{50} was found to be 2228.87 nM for the compounds in transitional range.

Model based upon *Superadjacency topochemical index*:

- Out of total 42 compounds, 25 compounds were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 88.0% with regard to CDK2/cyclin A inhibitory activity.
- The active range had *superadjacency topochemical index* values greater than 27.30 to 29.67. 9 out of 11 compound in the active range exhibited CDK2/cyclin A inhibitory activity. The average IC_{50} of the correctly predicted compounds was 52.2 nM, indicating high potency of the active range.
- Two inactive ranges with index values of <25.35 for lower inactive range and >32.74 for upper inactive range were observed. Though all the nine compounds in the lower inactive range were found to be inactive but only one compound in the upper inactive range exhibited biological activity. Average IC_{50} values of the order of 5387 and 5375 nM were observed for the lower inactive and upper inactive ranges respectively.
- Active range was ideally bracketed by two transitional ranges having superadjacency topochemical index values of 25.35 to 27.29 and 29.68 to 32.74. Existence of these transitional ranges indicates gradual change of biological activity. The average IC_{50} was found to be 1983 nM for the compounds in lower transitional range and 337.54 nM for the compounds in upper transitional range.

All the three topochemical models exhibited high accuracy of prediction ranging from 86% in case of Wiener's topochemical index to a maximum of 89% in case of atomic molecular connectivity index. This percentage has been derived from the ratio of the total number of compounds predicted correctly with respect to the assigned biological activity, to that of the total number of compounds present in both the active and inactive ranges. In the models based upon Wiener's topochemical index and AMCI, the active and inactive ranges are separated by a transitional range. Existence of such a transitional range is *ideal* because it simply indicates a gradual change in biological activity as one proceeds from active to inactive range and *vice versa*. The model based upon the superadjacency topochemical index is different from the other two models since this model has two inactive ranges and each one is separated from the active range by a transitional range. One of the appreciative features of all these models is the exceptionally high potency of the active ranges. Further, analysis of the structures of compounds in the active ranges reveals that the active ranges comprise mainly of 3-phenylacetamide derivatives. This is in line with the reported[38] structure–activity relationship of these compounds. When compared to the 3-propylamido and 3-benzamido aminopyrazoles (compounds **1**—**29**), 3-phenylacetamido derivatives (compounds **30**—**42**) have been reported to have potent cellular activities, because the former compounds displayed weak activity in tumor anti-proliferation test despite good activity in biochemical assay for CDK2/cyclin A.

Conclusion

The results indicate that the proposed models, based upon topochemical indices, have good predictability. These models may prove to be highly useful in prediction of activities of this series of compounds prior to synthesis. These models offer vast potential for lead optimization and may prove to be highly beneficial in the development of potent anti-tumor

agents.

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